REMARKS

I. Status Summary

Claims 1-100 are pending in the instant application and have been examined by the U.S. Patent and Trademark Office (hereinafter "the Patent Office"). Claims 1-6, 14-58, and 60-100 have been withdrawn from consideration as being drawn to unelected inventions. Claims 7-13 and 59 have been examined.

The specification has been objected to for the presence of browser-executable code (URL's).

Claims 7-13 and 59 have been objected to for encompassing non-elected inventions (SEQ ID NOs: 3-10). Claim 59 has been objected to for depending from a non-elected claim.

Claims 7-13 and 59 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specification, while enabling for SEQ ID NO: 15, is non-enabling for a polypeptide encoded by a nucleic acid sequence having 75% or more sequence identity to the nucleotide sequence of SEQ ID NO: 15. These same claims have also been rejected under this section upon the contention that the specification does not enable fragments of SEQ ID NO: 15. Additionally, these claims have been rejected under this section upon the contention that the specification does not enable a polypeptide encoded by a nucleic acid molecule capable of hybridizing under stringent conditions to a nucleic acid molecule comprising the first 434 nucleotides of SEQ ID NO: 15.

Claims 7-13 and 59 have been rejected under 35 U.S.C. §102(b) as anticipated by Stausberg (1998, Accession No. AI313496; hereinafter "AI313496"). The Patent Office contends that AI313496 is a DNA that is more than 60% homologous to a polynucleotide that hybridizes under stringent conditions to the first 434 nucleotides of SEQ ID NO: 15. These same claims are also rejected under this section as anticipated by Gu *et al.* (1996, Accession No. AAA99416; hereinafter "AAA99416"). According to the Patent Office, AAA99416 teaches a polynucleotide that includes part or all of the first 434 nucleotides of SEQ ID NO: 15, since "part or all" can mean very small fragments or even single nucleotides.

Claims 7-13 and 59 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that the phrase "stringent conditions" is indefinite.

The specification and claims 7, 9, 10, and 59 have been amended. Support for the amendments can be found throughout the specification as filed, including *inter alia* at page 41, lines 7-13 (90% identity of nucleic acid sequences). Additional support can be found at page 41, lines 13-17 (peptide identity of at least 65%), within the Sequence Listing (nucleotides 1-434, more particularly nucleotides 165-434, of SEQ ID NO: 15 encode amino acids 1-90 of SEQ ID NO: 16). Further support for the amendment to claim 7, subsection (e), regarding SEQ ID NO: 116 as a KCC3-specific sequence that can be used to raise antibodies against KCC3 polypeptides can be found in Figure 8, Example 21, and the Sequence Listing. With regard to this last point, the Patent Office's attention is directed to SEQ ID NOs: 3-10, 15, 16, and 116, review of which shows that the sequence presented in SEQ ID NO: 116 (KKARNAYLNNSNYEEGDEY) is found in SEQ ID NOs: 3-10, 15, and 16.

New claims 101-103 have been added. Support for the new claims can be found throughout the specification as filed, including particularly in the claims as originally filed (original claim 12 rewritten as claim 101). Additional support can be found at page 51, line 16, through page 52, line 2 (recombinant expression vectors), in the Sequence Listing (nucleotides 165-434 of SEQ ID NO: 15 encode amino acids 1-90 of SEQ ID NO: 16), and at page 64, lines 17-23 (100 nucleotide contiguous stretch of SEQ ID NO: 15). No new matter has been added. Reconsideration of the application as amended and based on the remarks set forth herein below is respectfully requested.

II. Response to the Objection to the Specification

The specification has been objected to for the presence of browser-executable code (URL's). Applicants have reviewed the specification and determined that URL's appear on pages 45, 107, and 111 (several instances). For each occurrence, applicants have amended the specification to refer to websites using only non-executable code. Please note that in the marked-up version of the rewritten paragraphs, language to be deleted has been struck-through. No additional language is

to be added, and the underlining under the words "See" appears in the original version of these paragraphs. Applicants respectfully submit that as a result of the amendments, the instant objection has been addressed. Applicants respectfully request the withdrawal of the objection.

III. Response to the Objection to the Claims

Claims 7-13 and 59 have been objected to for encompassing non-elected inventions (SEQ ID NOs: 3-10). Claim 59 has been objected to for depending from a non-elected claim. After careful consideration of the objections and the Patent Office's bases therefore, applicants respectfully traverse the objections and submit the following remarks.

The Patent Office has objected to the claims as encompassing non-elected inventions and/or depending from withdrawn claims. Applicants respectfully reiterate their traversal of the restriction requirement with regard to the Patent Office's contentions that the examination of SEQ ID NOs: 3-10, 15, and 16 presents an undue burden on the Patent Office. According to the Manual of Patent Examining Procedure (hereinafter "the MPEP") § 803.04, "It has been determined that normally ten sequences constitute a reasonable number for examination purposes. Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction". In response to the Restriction Requirement, applicants previously amended claim 7 to recite five nucleotide sequences and the corresponding five amino acid sequences encoded thereby. As a result, applicants respectfully submit that the number of sequences presented in claim 7 "constitute a reasonable number for examination purposes".

Applicants further respectfully submit that the sequences disclosed as SEQ ID NOs: 3-10, 15, and 16 correspond to alternatively spliced forms of the human and mouse KCC3 genes. As disclosed in the instant specification, the KCC3 gene encodes certain alternatively spliced forms, denoted as KCC3a and KCC3b. Additionally, a further alternatively spliced form similar to the KCC3a transcript but lacking coding exon 2 has been identified in both human and mouse, denoted as hKCC3a-X2 or hKCC3a2m

and mKCC3a-X2 or mKCC3a2m, respectively. These are the sequences disclosed as SEQ ID NOs: 3-10, 15, and 16 as follows:

Source and Splice Version	Nucleic acid SEQ ID NO.	Amino acid SEQ ID NO.
human KCC3a	15	16
human KCC3a – exon 2	5	6
mouse KCC3a	7	8
mouse KCC3a – exon 2	3	4
mouse KCC3b	9	10

Applicants respectfully submit that the Patent Office is misstating the teachings of the specification as to the various KCC polypeptides disclosed. Initially, applicants direct the Patent Office's attention to the above Table, in which it is shown that the polypeptides that the applicants are asserting should be examined together are all various isoforms of KCC3. These isoforms of KCC3, including particularly the KCC3a, KCC3b, and KCC3a – exon 2 from human and mouse, differ only in the composition of the intracellular N-terminus of the KCC3 protein, meaning that the central core of the transmembrane domains for each of these proteins are identical (or functionally identical, in the case of the human and mouse paralogs).

Furthermore, applicants respectfully submit that the Patent Office has misinterpreted the showing in Figure 8 as to SEQ ID NOs: 3-10, 15, and 16. These SEQ ID NOs refer to KCC3 polypeptides only. Figure 8, on the other hand, shows that there are differences in the characteristics of the paralogous KCCs (*i.e.* xKCC vs. KCC2 or KCC4).

Continuing, applicants respectfully submit that the Patent Office's reference to Figure 27D does not support the conclusion that searching all of the KCC3 sequences claimed in the application would present an undue burden on the Patent Office. Figure 27D simply shows that an antibody raised against an epitope in the amino-terminus of KCC3 does not cross-react with the KCC1, KCC2, or KCC4 polypeptides tested. Additionally, the sequence disclosed in SEQ ID NO: 116 corresponds to a KCC3-

specific antigen that can be found in both mouse and human KCC3s, including those disclosed in SEQ ID NOs: 3-10, 15, and 16.

And finally, applicants respectfully submit that the structures and percent identities between the mouse and human polypeptides disclosed mark them as orthologs. For example, mouse KCC3a has an N-terminal extension that is also found in the human KCC3a, both of which are encoded by orthologous exons (exon 1a) at analogous positions in the genes. Also, the human KCC3 gene (SLC12A6) and mouse KCC3 (Slc12a6) genes are found at syntenic regions of the mouse and human genomes, at chromosomes 2 and 15, respectively.

Accordingly, applicants respectfully submit the nucleic acid and amino acid sequences presented in SEQ ID NOs: 3-10, 15, and 16 correspond to human and mouse KCC3 gene products, and further that it would not present an undue burden on the Patent Office to search these five nucleic acid sequences and 5 amino acid sequences together. Thus, applicants respectfully request that SEQ ID NOs: 3-10, 15, and 16 be rejoined to claims 7, 9, and 10.

In the alternative, even assuming *arguendo* that these ten sequences present an undue search burden, applicants respectfully submit that SEQ ID NO: 15 recites the nucleic acid sequence of a human KCC3a splice variant, and SEQ ID NO: 7 recites the nucleic acid sequence of a murine homolog of this gene. Comparison of these sequences using the BLAST algorithm demonstrates that the nucleic acid sequence of the open reading frames of these sequences are at least 90% identical, and that the amino acid sequences of the encoded proteins are at least 97% identical. Applicants respectfully submit that at a minimum, SEQ ID NOs: 7, 8, 15, and 16 can be examined together without causing an undue burden on the Patent Office. Accordingly, applicants respectfully request that at a minimum, the Patent Office appropriately rejoin SEQ ID NOs: 7 and 8 to claims 7 and 10.

If the Patent Office refuses to rejoin any of the additional sequences to the application, in the alternative and in an effort to expedite prosecution of the instant claims, applicants have amended claims 7, 9, and 10 to recite SEQ ID NOs: 15 and 16, and sequences at least 90% or 65% identical to SEQ ID NOs: 15 and 16, respectively.

Support for these amendments can be found in the specification as filed, including particularly at page 41, lines 8-17. Applicants believe that these amendments address the objection to claims 7-13.

With regard to claim 59, applicants have amended claim 59 to depend solely from claim 7. Applicants believe that the removal of the multiple dependency of this claim from non-elected claims addresses the instant objection.

Accordingly, applicants respectfully submit that the objections to claims 7-13 and 59 have been addressed. Claim 12 has been canceled, and thus the objection as to this claim is believed to have been rendered moot. As a result, applicants respectfully request the withdrawal of the instant objections of claims 7-11, 13, and 59.

IV. Response to the Rejections Under 35 U.S.C. §112, First Paragraph

Claims 7-13 and 59 have been rejected under 35 U.S.C. § 112, first paragraph, on three bases. According to the Patent Office, the specification fails to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, for the reasons set out on pages 4-9 of the Official Action. Summarily, the Patent Office first asserts that the specification, while enabling for SEQ ID NO: 15, is non-enabling for a polypeptide encoded by a nucleic acid sequence having 75% or more sequence identity to the nucleotide sequence of SEQ ID NO: 15. Second, the Patent Office asserts that the specification does not enable fragments of SEQ ID NO: 15. And third, the Patent Office asserts that the specification does not enable a polypeptide encoded by a nucleic acid molecule capable of hybridizing under stringent conditions to a nucleic acid molecule comprising the first 434 nucleotides of SEQ ID NO: 15. After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

Applicants have amended claim 7 to recite the following: an isolated and purified nucleic acid molecule encoding a biologically active KCC3 potassium-chloride cotransporter polypeptide selected from the group consisting of:

(a) a biologically active KCC3 polypeptide encoded by a nucleic acid sequence as set forth in SEQ ID NO 15;

(b) a biologically active KCC3 polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence having 90% or greater sequence identity to SEQ ID NO 15;

(c) a biologically active KCC3 polypeptide having an amino acid sequence as set forth in SEQ ID NO 16;

(d) a biologically active KCC3 polypeptide comprising an amino acid sequence at least 65% identical to SEQ ID NO: 16; and

(e) a biologically active KCC3 polypeptide which is immunologically cross-reactive with an antibody which binds to an antigen having an amino acid sequence as set forth in SEQ ID NO: 116.

Initially, applicants respectfully submit that claim 7 is directed *inter alia* to nucleic acid molecules encoding biologically active KCC3 potassium-chloride cotransporter polypeptides. These biologically active KCC3 polypeptides include those encoded by a nucleic acid having 90-100% sequence identity to SEQ ID NO: 15, those with an amino acid sequence 65-100% identical to SEQ ID NO: 16, and those that bind to antibodies that bind to a SEQ ID NO: 116.

While applicants respectfully disagree with the Patent Office's assertions regarding the claim as originally filed, applicants submit the instant amendment in an effort to facilitate prosecution of the pending claims. In particular, applicants have amended claim 7 to recite a 90% or greater nucleotide sequence identity instead of a 75% or greater sequence identity. Applicants respectfully submit that amended claim 7 now essentially recites isolated and purified nucleic acid molecules encoding biologically active KCC3 potassium-chloride cotransporter polypeptides that are: (i) encoded by SEQ ID NO: 15 (subsection (a)); (ii) have the amino acid sequence of SEQ ID NO: 16 (subsection (c)); (iii) include a biological equivalent of the first amino acids of SEQ ID NO: 16 (subsections (b) and (d)); and/or are immunologically cross-reactive with an antibody which binds to an antigen having an amino acid sequence as set forth in SEQ ID NO: 116 (subsection (e)).

Furthermore, applicants respectfully submit that even assuming *arguendo* that some polynucleotides that are at least 90% identical to SEQ ID NO: 15 encode

nonfunctional polypeptides, the presence of nonfunctional embodiments does not render the specification non-enabling. With respect to the "percent identity" element, applicants respectfully submit that one of ordinary skill in the art can construct nucleic acid molecules that fall within the scope of the claim and, upon review of the guidance provided by the present specification, can thereafter determine the percent identity between the nucleic acid sequence of the constructed molecule and SEQ ID NO: 15 (and in addition, the amino acid sequence encoded therein in comparison to SEQ ID NO: 16) without undue experimentation. Having done so, one of ordinary skill in the art can also determine whether or not the polypeptide having or encoded by that sequence is a biologically active KCC3 potassium-chloride cotransporter, such as by employing the assays disclosed in Examples 12 *et seq.* of the instant patent application.

And finally, with respect to the Patent Office's contention that claim 7 "encompasses numerous undefined variants that will immunoreact to an antibody made against fragments of SEQ ID NO: 16, applicants respectfully submit the following. Initially, applicants respectfully submit that the claim taken in its entirety recites that the claimed nucleic acid must encode a biologically active KCC3 polypeptide. Furthermore, applicants respectfully submit that SEQ ID NO: 116 recites an N-terminal amino acid sequence that is specific for KCC3 from mouse and human. Given the discussion hereinabove, applicants respectfully submit that the instant specification (for example, Figures 8 and 27 and Examples 12 *et seq.*) adequately enables one of ordinary skill in the art to identify those nucleic acids that (a) encode a polypeptide that cross-reacts with an antibody that binds to SEQ ID NO: 16; and (b) itself encodes a biologically active KCC3.

Accordingly, applicants respectfully submit that all aspects of the current rejection have been addressed. Claim 12 has been canceled, and thus the instant rejection is believed to have been rendered moot as to this claim. Applicants thus respectfully request the withdrawal of the rejection of claims 7-11, 13, and 59 under 35 U.S.C. § 112, first paragraph. Allowance of claims 7-11, 13, and 59 is also respectfully requested.

V. Response to the Rejections Claims Under 35 U.S.C. §102(b)

The Patent Office has rejected claims 7-13 and 59 under 35 U.S.C. § 102(b) based on GenBank® Accession No. AI313496 by Strausberg (hereinafter "AI313496."). According to the Patent Office, AI313496 teaches a DNA that is more than 60% homologous to a polynucleotide that hybridizes under stringent conditions to a nucleic acid comprising the first 434 nucleotides of SEQ ID NO: 15. Claims 7-13 and 59 have also been rejected under 35 U.S.C. § 102(b) based on GenBank® Accession No. AAA99416 by Gu *et al.* (hereinafter "AAA99416."). According to the Patent Office, AAA99416 teaches an FMR2 polynucleotide that includes part or all of the first 434 nucleotides of SEQ ID NO: 15 since "part or all" can mean very small fragments or even single nucleotides. After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

Initially, applicants respectfully submit that the Patent Office asserts that AI313496 teaches a DNA that is more than 60% homologous to a polynucleotide that hybridizes under stringent conditions to a nucleic acid comprising the first 434 nucleotides of SEQ ID NO: 15. However, the Patent Office does not identify any such sequence. Furthermore, the sequence disclosed at AI313496 shows no significant similarity to SEQ ID NO: 15 itself when examined using the BLAST algorithm available at the website of the National Center for Biotechnology Information (NCBI). Applicants respectfully submit that that the Patent Office has not met its burden in establishing a *prima facie* case of anticipation simply by stating that the cited sequence falls within the limits of the claims. As a result, applicants respectfully request the withdrawal of the instant rejection.

Furthermore, applicants respectfully submit that claim 7 recites an isolated and purified nucleic acid molecule encoding a biologically active KCC3 potassium-chloride cotransporter polypeptide. Given that AI313496 does not encode a biologically active KCC3 polypeptide, applicants respectfully submit that AI313496 does not anticipate claim 7, and further that since claims 8-13 and 59 depend directly or indirectly from claim 7, these claims are not anticipated by AI313496. Accordingly, applicants

respectfully request the withdrawal of the first rejection of claims 7-13 and 59 under § 102(b).

With regard to the second rejection of claims 7-13 and 59 under § 102(b), applicants respectfully submit that AAA99416 teaches an FMR2 polynucleotide that shows no homology whatsoever to the polynucleotides recited in claim 7. Furthermore, AAA99416 does not encode a biologically active KCC3 potassium-chloride cotransporter polypeptide. For these two reasons, applicants respectfully submit that AAA99416 does not anticipate claim 7.

Claim 7 is believed to be distinguished from the cited art of record. Claims 8-13 depend either directly or indirectly from claim 7, and thus are also believed to be patentably distinguished from the cited art of record. Claim 12 has been canceled, and thus applicants believe that the rejection has been rendered moot as to this claim. As a result, applicants respectfully submit that the rejections of claims 7-11, 13, and 59 under 35 U.S.C. § 102(b) has been addressed, and respectfully request that the rejections be withdrawn and the claims be allowed at this time.

VI. Response to Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 7-13 and 59 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that the phrase "stringent conditions" is a conditional term. After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that that the Patent Office's contention that the phrase "stringent conditions" is indefinite because "some nucleic acids which are able to hybridize under stringent conditions would be unable to hybridize under non-stringent conditions" is unclear. For example, the Patent Office has not indicated under what "non-stringent" conditions two nucleic acid molecules that could hybridize under stringent conditions would fail to hybridize. Nonetheless, in an effort to expedite prosecution of the pending claims, applicants have amended claim 7 to remove the recitation of "stringent conditions".

Accordingly, applicants respectfully submit that the rejection of claims 7-13 and 59 has been addressed by the amendment to claim 7. Claim 12 has been canceled, and thus applicants believe that the rejection has been rendered moot as to this claim. Applicants respectfully submit that claims 7-11, 13, and 59 are now in condition for allowance, and earnestly solicit a Notice of Allowance to that effect.

VII. New Claims

New claims 101-103 have been added. Support for the new claims can be found throughout the specification as filed, including particularly in the claims as originally filed (original claim 12 rewritten as claim 101). Additional support can be found at page 51, line 16, through page 52, line 2 (recombinant expression vectors), in the Sequence Listing (nucleotides 165-434 of SEQ ID NO: 15 encode amino acids 1-90 of SEQ ID NO: 16), and at page 64, lines 17-23 (100 nucleotide contiguous stretch of SEQ ID NO: 15). Applicants respectfully submit that no new matter has been added as a result of the addition of new claims 101-103. Applicants further respectfully submit that new claims 101-103 are patentably distinguishable over the references cited by the Patent Office for the reasons set forth hereinabove with regard to claim 7 as claims 101-103 depend directly or indirectly from claim 7. Applicants also respectfully submit that claims 101-103 are in condition for allowance, and earnestly solicit a Notice of Allowance to that effect.

CONCLUSIONS

In light of the above amendments and remarks, applicants submit that the subject patent application is in condition for allowance and courteously solicit a Notice of Allowance.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

Deposit Account

The Commissioner is hereby authorized to charge any deficiencies of payment associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

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